PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

MONEY
ORDER
DIARY 18/12/02
REC'D (LONDON) 21 NOV 2002
ANSO
ENTRY
FOR CLM

SOUTHAMPTON
21 NOV 2002

PCT

To:
D YOUNG & CO
Attn. Mallalieu, Catherine L.
21 New Fetter Lane
London EC4A 1DA
UNITED KINGDOM

INVITATION TO PAY ADDITIONAL FEES

(PCT Article 17(3)(a) and Rule 40.1)

REGISTERED MAIL

Applicant's or agent's file reference P011069WO CLM	Date of mailing *(day/month/year)* 18/11/2002
International application No. PCT/GB 02/ 03381	**PAYMENT DUE** within 30 ~~months~~/days from the above date of mailing
Applicant LORANTIS LIMITED	International filing date *(day/month/year)* 25/07/2002

1. This International Searching Authority

(i) considers that there are 63 *(number of)* inventions claimed in the international application covered by the claims indicated ~~below~~/on the extra sheet:

and it considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated ~~below~~/on the extra sheet:

(ii) [X] has carried out a partial international search (see Annex) [ ] will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.:
see form PCT/ISA/206

(iii) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid

2. The applicant is hereby **invited,** within the time limit indicated above, to pay the amount indicated below:

EUR 945,00 (Fee per additional invention) x 62 (number of additional inventions) = EUR 58.590,00 (total amount of additional fees)

Or, _____ x _____ = _____

The applicant is informed that, according to Rule 40.2(c), **the payment of any additional fee may be made under protest,** i.e., a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fee is excessive.

3. [X] Claim(s) Nos. s. PCT/ISA/206 have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Anna Sjlberg

Form PCT/ISA/206 (July 1992)

INVITATION TO PAY ADDITIONAL FEES

International application No.
PCT/GB 02/03381

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Inventions 1 (Claims 1-6, 16-18 and 25-35)

A conjugate comprising first and second sequences wherein the first sequence comprises a polypeptide which is capable of binding to an antigen presenting cell (APC) surface molecule MHC class II, or is a polynucleotide which encods therefor, and a second sequence comprises a polypeptide capable of modulating of a T cell signalling pathway according to claims 2-5, wherein it is Notch or a fragment thereof which retains the siganlling transduction ability of Notch or an analogue of Notch which has the siganlling transduction ability of Notch or a polynucleotide sequence which encods therefor, expression vectors comprising corresponding sequences according to claim 26 and the corresponding sequences accorrding to claim 26, hosts according to cliam 27, a method of preparing the conjugates according to calim 28, conjugates according to claim 29, methods of targeting a protein for notch signalling modulation according to claim 30, pharmaceutical compositins according to claims 31,32, uses of the conjugates according to claims 33,34, and products according to claim 35, respectivelly.

Inventions 2-14 (Claims 1-6, 16-18 and 25-35)

A conjugate comprising first and second sequences wherein the first sequence comprises a polypeptide which is capable of binding to an antigen presenting cell (APC) surface molecule sellected from the group consisitng of the following 13 further embodimnets, in respect to each invention: CD205, CD204, CD14, CD206, TLR, CD207, CD209, Fc gamma receptor, CD68, CD83, CD33, CD54 or BDCA-2,3,4, or is a polynucleotide which encods therefor, and a second sequence comprises a polypeptide capable of modulating of a T cell signalling pathway according to claims 2-5, wherein it is Notch or a fragment thereof which retains the siganlling transduction ability of Notch or an analogue of Notch which has the siganlling transduction ability of Notch or a polynucleotide sequence which encods therefor, expression vectors comprising corresponding sequences according to claim 26 and the corresponding sequences accorrding to claim 26, hosts according to cliam 27, a method of preparing the conjugates according to calim 28, conjugates according to claim 29, methods of targeting a protein for notch signalling modulation according to claim 30, pharmaceutical compositins according to claims 31,32, uses of the conjugates according to claims 33,34, and products according to claim 35, respectivelly.

Invention 15 (Claims 1-6, 16-24 and 25-35)

A conjugate comprising first and second sequences wherein

the first sequence comprises a polypeptide which is capable of binding to an antigen presenting cell (APC) surface molecule wherein the sequence is derived from superantigen according to claims 19-24, or is a polynucleotide which encods therefor, and a second sequence comprises a polypeptide capable of modulating of a T cell signalling pathway according to claims 2-5, wherein it is Notch or a fragment thereof which retains the siganlling transduction ability of Notch or an analogue of Notch which has the siganlling transduction ability of Notch or a polynucleotide sequence which encods therefor, expression vectors comprising corresponding sequences according to claim 26 and the corresponding sequences accorrding to claim 26, hosts according to cliam 27, a method of preparing the conjugates according to calim 28, conjugates according to claim 29, methods of targeting a protein for notch signalling modulation according to claim 30, pharmaceutical compositins according to claims 31,32, uses of the conjugates according to claims 33,34, and products according to claim 35, respectivelly.

Inventions 16-30 (claims 1-5,7,8,16-18 and 25-35)

A conjugate comprising first and second sequences wherein the first sequence comprises a polypeptide which is capable of binding to an antigen presenting cell (APC) surface molecule sellected from the group consisitng of the following 14 embodimnets, in respect to each invention: MHC class II, CD205, CD204, CD14, CD206, TLR, CD207, CD209, Fc gamma receptor, CD68, CD83, CD33, CD54 or BDCA-2,3,4, or is a polynucleotide which encods therefor, and a second sequence comprises a polypeptide capable of modulating of a T cell signalling pathway according to claims 2-5, wherein it is Notch ligand or a fragment thereof which retains the siganlling transduction ability of Notch ligand or an analogue of Notch ligand which has the siganlling transduction ability of Notch ligandor a polynucleotide sequence which encods therefor, wherein the sequence is derived from Delta or Serrate, expression vectors comprising corresponding sequences according to claim 26 and the corresponding sequences accorrding to claim 26, hosts according to cliam 27, a method of preparing the conjugates according to calim 28, conjugates according to claim 29, methods of targeting a protein for notch signalling modulation according to claim 30, pharmaceutical compositins according to claims 31,32, uses of the conjugates according to claims 33,34, and products according to claim 35, respectivelly.

Invention 31 (claims 1-5,7,8,16-24 and 25-35)

A conjugate comprising first and second sequences wherein the first sequence comprises a polypeptide which is capable of binding to an antigen presenting cell (APC) surface molecule wherein the sequence is derived from superantigen

according to claims 19-24, or is a polynucleotide which encods therefor, and a second sequence comprises a polypeptide capable of modulating of a T cell signalling pathway according to claims 2-5, wherein it is Notch ligand or a fragment thereof which retains the siganlling transduction ability of Notch ligand or an analogue of Notch ligand which has the siganlling transduction ability of Notch ligandor a polynucleotide sequence which encods therefor, wherein the sequence is derived from Delta or Serrate, expression vectors comprising corresponding sequences according to claim 26 and the corresponding sequences accorrding to claim 26, hosts according to cliam 27, a method of preparing the conjugates according to calim 28, conjugates according to claim 29, methods of targeting a protein for notch signalling modulation according to claim 30, pharmaceutical compositins according to claims 31,32, uses of the conjugates according to claims 33,34, and products according to claim 35, respectivel

Inventions 32-46 (claims 1-5,9-11,16-18 and 25-35)

A conjugate comprising first and second sequences wherein the first sequence comprises a polypeptide which is capable of binding to an antigen presenting cell (APC) surface molecule sellected from the group consisitng of the following 14 embodimnets, in respect to each invention: MHC class II, CD205, CD204, CD14, CD206, TLR, CD207, CD209, Fc gamma receptor, CD68, CD83, CD33, CD54 or BDCA-2,3,4, or is a polynucleotide which encods therefor, and a second sequence comprises a polypeptide capable of modulating of a T cell signalling pathway according to claims 2-5, wherein it is capable of upregulating the expression or acitivity of Notch or a Notch ligand or a downstream component aof the siganlling transduction pathway, an antibody or the embodiments of Claims 10-11 or a polynucleotide sequence which encods therefor, expression vectors comprising corresponding sequences according to claim 26 and the corresponding sequences accorrding to claim 26, hosts according to cliam 27, a method of preparing the conjugates according to calim 28, conjugates according to claim 29, methods of targeting a protein for notch signalling modulation according to claim 30, pharmaceutical compositins according to claims 31,32, uses of the conjugates according to claims 33,34, and products according to claim 35, respectivelly.

Invention 47 (claims 1-5,9-11,16-24 and 25-35)

A conjugate comprising first and second sequences wherein the first sequence comprises a polypeptide which is capable of binding to an antigen presenting cell (APC) surface molecule wherein the sequence is derived from superantigen according to claims 19-24, or is a polynucleotide which encods therefor, and a second sequence comprises a

polypeptide capable of modulating of a T cell signalling pathway according to claims 2-5, wherein it is capable of upregulating the expression or acitivity of Notch or a Notch ligand or a downstream component aof the siganlling transduction pathway, an antibody or the embodiments of Claims 10-11 or a polynucleotide sequence which encods therefor, expression vectors comprising corresponding sequences according to claim 26 and the corresponding sequences accorrding to claim 26, hosts according to cliam 27, a method of preparing the conjugates according to calim 28, conjugates according to claim 29, methods of targeting a protein for notch signalling modulation according to claim 30, pharmaceutical compositins according to claims 31,32, uses of the conjugates according to claims 33,34, and products according to claim 35, respectivelly.

Inventions 48-62 (claims 1-5,12-15,16-18 and 25-35)

A conjugate comprising first and second sequences wherein the first sequence comprises a polypeptide which is capable of binding to an antigen presenting cell (APC) surface molecule sellected from the group consisitng of the following 14 embodimnets, in respect to each invention: MHC class II, CD205, CD204, CD14, CD206, TLR, CD207, CD209, Fc gamma receptor, CD68, CD83, CD33, CD54 or BDCA-2,3,4, or is a polynucleotide which encods therefor, and a second sequence comprises a polypeptide capable of modulating of a T cell signalling pathway according to claims 2-5, wherein it is capable of Notch siganlling inhibition or downregulation of Notch according to claims 12-15 or a polynucleotide sequence which encods therefor, expression vectors comprising corresponding sequences according to claim 26 and the corresponding sequences accorrding to claim 26, hosts according to cliam 27, a method of preparing the conjugates according to calim 28, conjugates according to claim 29, methods of targeting a protein for notch signalling modulation according to claim 30, pharmaceutical compositins according to claims 31,32, uses of the conjugates according to claims 33,34, and products according to claim 35, respectivelly.

Invention 63 (claims 1-5,12-15,16-24 and 25-35)

A conjugate comprising first and second sequences wherein the first sequence comprises a polypeptide which is capable of binding to an antigen presenting cell (APC) surface molecule wherein the sequence is derived from superantigen according to claims 19-24, or is a polynucleotide which encods therefor, and a second sequence comprises a polypeptide capable of modulating of a T cell signalling pathway according to claims 2-5, wherein it is capable of Notch siganlling inhibition or downregulation of Notch according to claims 12-15 or a polynucleotide sequence which encods therefor, expression vectors comprising corresponding

sequences according to claim 26 and the corresponding sequences accorrding to claim 26, hosts according to cliam 27, a method of preparing the conjugates according to calim 28, conjugates according to claim 29, methods of targeting a protein for notch signalling modulation according to claim 30, pharmaceutical compositins according to claims 31,32, uses of the conjugates according to claims 33,34, and products according to claim 35, respectivelly.

The present application does not comply with the requirements of unity of invention. At least 63 separate inventions have been identified. Each of them is characterised by an individual "special technical feature"; there is no technical interrelation between these inventions (see below). The applicants are therefore asked to pay additional search fees. Otherwise the International Search Report will be limited to the first invention specified above 'Art. 17(3)(a) PCT; Rule 13(1) PCT; Rule 40 PCT!.

The following arguments reflect the preliminary opinion of the ISA concerning unity of invention:

Rule 13(2) PCT demands that "Rule 13.1 PCT shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression 'special technical features' shall mean those technical features which define a contribution which each of the claimed invention considered as a whole makes over the prior art." The PCT Preliminary Examination Guidelines C-III 7.6 state more precisely that "if the common matter of the independent claim is well known, and the remaining subject-matter ... differs without there being any unifying novel concept common to all of them, then clearly there is lack of unity".

The presently claimed subject-matter does not fulfil the necessary requirements on unity of invention as outlined above:

In view of the disclosure of the present application, the technical problem to be solved is the following: Provision of further diagnostic or therapeutic compositions useful in the detection, prevention and treatment of T cell mediated diseases or disorders (page 2, lines 16-18). The present application provides such further composition based on a conjugate comprising first and second sequences wherein the first sequence comprises a polypeptide which is capable of binding to an antigen presenting cell (APC) or a polynucleotide encoding therefor, and the second sequence comprises a polypeptide capable of modulating of a T cell signalling pathway, or polynucleotide coding therefor (page 78, Claim 1). In the dependent claims more specific embodiments of the first and second sequence are disclosed, such as a protein for Notch signalling transduction or a fragment thereof, in case of the second sequence (page 78, Claim 5) and such as a polypeptide which is capable of binding to Fc gamma-receptor on the surface of APC, in case of the first sequence (page 80, Claims 16 and 17).

Nonetheless, the alleged common technical feature of all solutions to the technical problem presented in the application is the conjugate comprising first and second sequences of Claim 1, as described above.

The available prior art discloses at least one such a conjugate of first and second sequence. WO9820142 on page 8 lines 9-11, and on page 31, claims 15-17, discloses a compound which is a fusion protein comprising a segment of Notch or Notch ligand extracellular domain and an immunoglobulin Fc segment, preferably, Ig gamma Fc. It is needles to state that Fc segment of Ig gamma is capable of binding to Fc gamma-receptor present on the surface of APC. The compound of WO9820142 is generated for the use in modulation of the therapy of conditions such as graft rejection, autoimmunity, allergy, asthma and infectious diseases by the way of mechanism of modifying T cell-APC interactions involving Notch signalling (Abstract).

From the fact that the fusion protein of WO9820142 described above has the essential technical features of the conjugate of present claim 1, (the one sequence of a polypeptide capable of binding to APC - Ig gamma Fc, and the other sequence of a polypeptide capable of modulating of a T cell signalling pathway - segment of Notch or Notch ligand) it follows that all of the solutions suggested in the present application have no "special technical feature" in common.

In view of the prior art (supra), the technical content of the present application has to be rearranged into at least 63 individual independent solutions to the objective technical problem of the provision of further conjugates comprising first and second sequences according to present Claim 1 (see above).

Having regard to the requirement set forth in Art.17(3)(a) PCT to establish the international search report on those parts of the international application which relate to the invention first mentioned in the claims, the examiner considers the following. In view of the combinatorial language used to formulate the present claims, which requires the juxtaposing of any of the various embodiments of the second sequence of the conjugate (claims 2-15) with any of the possible various embodiments of the first sequence of the conjugate, according to claims 16-24, the invention that is the first one is that listed as subject 1 above.

Due to the fact that the subject matter of claims 17(partly)-24, especially in combination of embodiments of claims 7-15 requires a separate search for the structural concept(s) and the covered compounds in databases and partially in the classified documentation, the ISA considers that the PCT Guideline VII, 12, regarding a complete search with negligible additional work, is certainly not applicable.

Paying an additional fee for further inventions without notice could result in a further declaration of lack of unity. Regarding the time constraints of the PCT procedure the applicant is therefore strongly urged to define for which unified subject matter of further inventions a further search should be established and to pay for each identified invention an additional search fee.

Please note also that Rule 13 PCT has a regulatory function (to prevent unjustified saving of fees, and to ensure ready comprehensibility). Also

from this more pragmatic approach the present application lacks unity of invention: First, due to the lack of constant characteristic "special technical features", competitors cannot inform themselves readily on the existing situation regarding protective rights. Second, the equitable levying of fees has to be respected. Because of its heterogeneous content, the present application entails a far greater than average expense in the procedure up to grant (keep in mind that there is an ample background concerning subject-matter with related technical and functional features, thus necessitating several independent searches of restricted scope).

Annex to Form PCT/ISA/206
COMMUNICATION RELATING TO THE RESULTS OF THE PARTIAL INTERNATIONAL SEARCH

International Application No
PCT/GB 02/03381

1. The present communication is an Annex to the invitation to pay additional fees (Form PCT/ISA/206). It shows the results of the international search established on the parts of the international application which relate to the invention first mentioned in claims Nos.:
see 'Invitation to pay additional fees'
2. This communication is not the international search report which will be established according to Article 18 and Rule 43.
3. If the applicant does not pay any additional search fees, the information appearing in this communication will be considered as the result of the international search and will be included as such in the international search report.
4. If the applicant pays additional fees, the international search report will contain both the information appearing in this communication and the results of the international search on other parts of the international application for which such fees will have been paid.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 20142 A (DALLMAN MARGARET JANE ;HOYNE GERALD FRANCIS (GB); IMPERIAL COLLEGE) 14 May 1998 (1998-05-14) cited in the application abstract page 1, line 10 - line 13 page 8, line 9 - line 11 page 31; claims 15-17 ---	1-6,16, 17,25-35
A	WO 00 36089 A (DALLMAN MARGARET JANE ;LORANTIS LTD (GB); HOYNE GERARD FRANCIS (GB) 22 June 2000 (2000-06-22) page 1 -page 7 -----	1-6,16, 17,25-35

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Patent Family Annex

Information on patent family members

International Application No
PCT/GB 02/03381

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9820142 A	14-05-1998	AU	736361 B2	26-07-2001
		AU	4876597 A	29-05-1998
		BG	103444 A	30-06-2000
		CZ	9901639 A3	13-10-1999
		EP	0942998 A1	22-09-1999
		GB	2353094 A ,B	14-02-2001
		WO	9820142 A1	14-05-1998
		GB	2335194 A ,B	15-09-1999
		JP	2001504331 T	03-04-2001
		NO	992196 A	05-07-1999
		NZ	335549 A	27-07-2001
		PL	333302 A1	22-11-1999
		TR	9901000 T2	21-07-1999
		HU	0001059 A2	28-08-2000
WO 0036089 A	22-06-2000	AU	1789500 A	03-07-2000
		EP	1141243 A2	10-10-2001
		WO	0036089 A2	22-06-2000

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 206

Continuation of Box 3.

Claims Nos.: 35(partly)

Present claim 35 does not define any essential features of the conjugate, polypeptide sequence, expression vector, host cell, method, pharmaceutical composition and use. Instead a reference is made for the essential features for which protection is sought to the accompanying figures and substantive description. Art. 5 PCT requires that the subject matter be defined in claims in a clear and concise manner. As claim 35 refers to the technical features present in the whole of the application, it is certainly not concise. Moreover, as the application contains a large number of different technical features, it is not clear which of them should be regarded as the essential features defining the subject matter.
Due to the lack of conciseness and clarity the subject matter of claim 35 was searched only in the sense of the features defined in the preceding claims 1-6,16-17 and 25-34.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.